## REMARKS

### I. STATUS AND AMENDMENTS TO THE CLAIMS

In this Amendment, claims 1, 3-5, 7-10, 12-17, 20-22, 46-49, 53-56, 61, and 66-69 are canceled, and claims 70-79 are new. After entry of this Amendment, claims 70-79 will be the only claims pending.

The format of independent claim 70 corresponds essentially to the independent claims of related co-pending applications 10/357,507, 10/338,044, and 10/152,319, which are allowed.

For the Examiner's convenience, the Table below outlines exemplary written description support for independent claim 70.

| **Claim 70** | **Exemplary Written Description Support** |
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| 70. A method for determining whether a test compound is a hepatotoxin, comprising:<br><br>(a) exposing liver tissue or liver cells to the test compound;<br><br>(b) preparing a normalized gene expression profile of at least ten genes for said liver tissue or liver cells, wherein the gene expression profile contains the differential gene expression levels for said at least ten genes upon exposure to the test compound, and wherein said at least ten genes are listed in one of Tables 5A-5WWW;<br><br>(c) comparing the gene expression profile to a hepatotoxicity model, the hepatotoxicity model comprising: | ABSTRACT<br>***The present invention is based on the elucidation of the global changes in gene expression and the identification of toxicity markers in liver tissues or cells exposed to a known toxin.*** The genes may be used as toxicity markers in drug screening and toxicity assays. ***The invention includes a database of genes characterized by liver toxin-induced differential expression*** that is designed for use with microarrays and other solid-phase probes.<br><br>[0012] The present inventors have examined tissue from animals exposed to the known hepatotoxins which induce detrimental liver effects, to identify global changes in gene expression and individual changes in gene expression induced by these compounds. ***These global changes in gene expression, which can be detected by the production of expression profiles,*** |

| Claim 70 | Exemplary Written Description Support |
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| (i) the normalized mean expression levels of said at least ten genes in liver tissue or liver cells exposed to a known hepatotoxin,<br><br>(ii) the normalized mean expression levels of said at least ten genes in unexposed liver tissue or liver cells, and<br><br>(iii) information from one or more of Tables 5A-5WWW; and<br><br>(d) scoring the comparison to determine whether the test compound is a hepatotoxin. | provide useful toxicity markers that can be used to monitor toxicity and/or toxicity progression by a test compound.<br><br>[0085] In general, assays to predict the toxicity or hepatotoxicity of a test agent (or compound or multi-component composition) comprise the steps of ***exposing a cell population to the test compound, assaying or measuring the level of relative or absolute gene expression of one or more of the genes in Tables 1-5WWW*** and comparing the identified expression level(s) to the expression levels disclosed in the Tables and database(s) disclosed herein. ***Assays may include the measurement of the expression levels of about 2, 3, 4, 5, 6, 7, 8, 9, 10, 15, 20, 25, 30, 50, 75, 100 or more genes from Tables 1-5WWW to create multi-gene expression profiles***.<br><br>[0086] In the methods of the invention, ***the gene expression level for a gene or genes induced by the test agent, compound or compositions may be comparable to the levels found in the Tables*** or databases disclosed herein if the expression level varies within a factor of about 2, about 1.5 or about 1.0 fold. In some cases, ***the expression levels are comparable if the agent induces a change in the expression of a gene in the same direction (e.g., up or down) as a reference toxin.***<br><br>[0110] ***The genes identified as being differentially expressed upon exposure to a known hepatotoxin (Tables 5A-5WWW)*** may be used in a variety of nucleic |

| Claim 70 | Exemplary Written Description Support |
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| | acid detection assays to detect or quantify the expression level of a gene or multiple genes in a given sample.<br><br>[0187] Tables 5A-5WWW disclose a core or alternate set of genes, along with the summary statistics for each of the comparisons performed as indicated in these tables- i. e. , expression levels of a particular gene in toxicity group samples compared to non- toxicity group samples in response to exposure to a particular toxin, or as measured in a particular disease state. ***Each of these tables contains a set of predictive genes and creates a model for predicting the hepatoxicity of an unknown, i. e. , untested compound.*** Each gene is identified by its Gene Logic identification number and can be cross-referenced to a gene name and representative SEQ ID NO. in Table 1 or in one more related applications, as mentioned on page 1. ***For each comparison of gene expression levels between samples in the toxicity group (samples affected by exposure to a toxin) and samples in the non-toxicity group (samples not affected by exposure to a toxin), the tox mean (for toxicity group samples) is the mean signal intensity, as normalized for the various chip parameters that are being assayed. The non-tox mean represents the mean signal intensity, as normalized for the various chip parameters that are being assayed, in non-toxicity group samples. For individual genes, an increase in the tox mean compared to the non-tox mean indicates up-regulation upon exposure to a toxin, while a decrease in the group mean compared to the non-group mean indicates down-regulation.*** |

| Claim 70 | Exemplary Written Description Support |
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| | [0203] The above modeling methods provide broad approaches of combining the expression of genes to predict sample toxicity. One method uses each variable individually and weights them; the other combines variables as a composite measure and adds weights to them after combination into a new variable. One could also provide no weight in a simple voting method or determine weights in a supervised or unsupervised method using agglomerate, divisive, or random approaches. All or selected combinations of genes may be combined in ordered, agglomerate, or divisive, supervised or unsupervised clustering algorithms with unknown samples for classification. Any form of correlation matrix may also be used to classify unknown samples. The spread of the group distribution and discriminate score alone provide enough information to enable a skilled person to generate all of the above types of models with accuracy that can exceed discriminate ability of individual genes. Some examples of methods that could be used individually or in combination after transformation of data types include but are not limited to: Discriminant Analysis, Multiple Discriminant Analysis, logistic regression, multiple regression analysis, linear regression analysis, conjoint analysis, canonical correlation, hierarchical cluster analysis, k-means cluster analysis, self- organizing maps, multidimensional scaling, structural equation modeling, support vector machine determined boundaries, factor analysis, neural networks, bayesian classifications, and resampling methods.<br><br>[0204] Samples were grouped into individual pathology |

| Claim 70 | Exemplary Written Description Support |
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| | classes based on known toxicological responses and observed clinical chemical and pathology measurements or into early and late phases of observable toxicity within a compound (Tables 1-5WWW).<br><br>[0205] ***Samples may be considered toxic if they score positive in any pathological or individual compound class represented here or in any modeling method mentioned under general toxicology models based on combination of individual time and dose grouping of individual toxic compounds obtainable from the data.*** The pathological groupings and early and late phase models are preferred examples of all obtainable combinations of sample time and dose points. Most logical groupings with one or more genes and one or more sample dose and time points should produce better predictions of general toxicity, pathological specific toxicity, or similarity to known toxicant than individual genes. |

Additional support (e.g., in addition to the above passages) for dependent claims 71-79 may be found in the original claims and disclosure as follows.

Claim 71 is supported by paragraphs [0085], [0187], and [0204] of the specification, for example.

Claim 72 is supported by original claim 54, and paragraphs [0110] and [0132] of the specification, for example.

Claim 73 is supported by the specification at paragraph [0187], for example.

Claim 74 is supported by original claim 53 and the Examples in the specification as filed.

Claim 75 is supported by original claims 20 and 21, for example.

Claim 76 is supported by original claim 47, for example.

Claims 77 and 78 are supported by paragraphs [0085], [0187], and [0204] of the specification, for example.

Claim 79 is supported by, for example, paragraphs [0086] and [0187].

No new matter has been introduced.

Entry and consideration of this Amendment are respectfully requested.

## II. RESPONSE TO OBJECTIONS TO THE SPECIFICATION

At page 2 of the Office Action, the Examiner objects to the hyperlinks in the specification. These have been deleted as required.

Also at page 2 of the Office Action, the Examiner objects to the title as not being sufficiently descriptive. The title has been amended as required.

Withdrawal of the objections is requested.

## III. RESPONSE TO OBJECTIONS TO THE CLAIMS

At page 2 of the Office Action, the Examiner objects to the misspelling of "hepaotoxin" in previous claim 1.

New claims have been added. The Applicant is not aware of any misspellings or grammatical errors in the new claims.

## IV. RESPONSE TO CLAIM REJECTIONS UNDER 35 USC §112, 1st PARAGRAPH

At pages 3-8 of the Office Action, previous claims 1, 3-5, 7, 9, 12-17, 20-22, 47-49, 53-56, 61, and 66 are rejected under 35 U.S.C. §112, first paragraph. Specifically, in the

Examiner's opinion, the specification does not clearly identify that the data in Tables 5A-5WWW was generated from liver tissue or liver cells, and because the claim language does not clearly recite the nature of the gene expression values that are being compared.

New claims 70-79 have been added to replace the original claims. New claims 70-79 are fully enabled by the specification.

First, the data set forth in the Tables was generated from liver tissue only, and thus, the expression levels provided in the Tables fully enable the invention as currently claimed. The origin of the data is set forth in the Abstract, for example, which states:

> The present invention is based on the elucidation of the global changes in gene expression and **the identification of toxicity markers in liver tissues or cells exposed to a known toxin**.

The fact that the data was generated in liver tissue or liver cells is further evident from the provisional applications to which this application claims priority, and which are incorporated by reference at paragraph [0001] of this application. See, for example, page 4, line 1, and Example 2 of Provisional Application No. 60/364,055, and the description of the Figures (and particularly Figures 2, 6-10, and 13) of Provisional Application No. 60/364,045.

Second, claims 70-79 recite preparing a "normalized gene expression profile" containing differential gene expression levels for the genes upon exposure to the test compound. Claims 70-79 further recite that the hepatotoxicity model comprises the "normalized mean expression levels" for the genes in liver tissue or liver cells exposed to a known hepatotoxin, and "the normalized mean expression levels" for the genes in unexposed liver tissue or liver cells. Thus, the new claims clearly set forth the nature of the values being compared.

Accordingly, claims 70-79 are fully enabled by the specification. Withdrawal of this rejection is respectfully requested.

V. RESPONSE TO REJECTION UNDER 35 USC §112, 2ND PARAGRAPH

At pages 8-10 of the Office Action, claims 1, 3-5, 7, 9, 12-17, 20-22, 47-49, 53-56, 61, and 66 are rejected under 35 USC §112, second paragraph, as being indefinite.

First, the Examiner asserts that the language "a method for predicting at least one toxic effect of a compound" is unclear, because the language is not consistent with the body of the claim.

The preamble and body of new independent claim 70 are consistently drawn to determining whether a test compound is a hepatotoxin.

Second, the Examiner asserts that the term "correspond" as originally recited in claims 3 and 7, is indefinite.

The new claims do not use the term "correspond."

Third, the Examiner asserts that the term "substantially," as originally recited in claim 5, is indefinite.

The new claims do not use the term "substantially."

Fourth, the Examiner asserts that the term "differential expression," as originally recited in claims 7 and 9, is indefinite, because only one gene expression value is detected.

The new claims recite that the differential gene expression levels are "upon exposure to the test compound," and therefore, the term "differential expression" is not indefinite.

Withdrawal of these rejections is respectfully requested.

VI. RESPONSE TO REJECTIONS UNDER 35 USC §101

At pages 10-12 of the Office Action, claims 1, 3-5, 7, 9, 12-17, 20-22, 47-49, 53-56, 61, and 66 are rejected under 35 USC §101, as allegedly being directed to non-statutory subject matter.

The new claims recite a step of "exposing" liver tissue or liver cells to a test compound, which results in a physical transformation of matter.

The new claims are therefore drawn to patentable subject matter.

Withdrawal of this rejection is respectfully requested.

## VII. PROVISIONAL OBVIOUSNESS-TYPE DOUBLE PATENTING REJECTIONS

At pages 12-19 of the Office Action, one or more of the previously pending claims are rejected for obviousness-type double patenting over one or more claims of co-pending application nos.: 10/357,507, 11/059,535, 10/515,373, and 11/547,759.

A Terminal Disclaimer is being submitted herewith to render moot the obviousness-type double patenting rejection over Application No. 10/357,507 (which has been allowed).

As to Application Nos. 11/059,535, 10/515,373, and 11/547,759, no response is believed to be necessary at this time. The Examiner's attention is respectfully directed to MPEP §804(I)(B):

> If a "provisional" nonstatutory obviousness-type double patenting (ODP) rejection is the only rejection remaining in the earlier filed of the two pending applications, while the later-filed application is rejectable on other grounds, the examiner should withdraw that rejection and permit the earlier-filed application to issue as a patent without a terminal disclaimer.

Thus, Applicants respectfully request that the obviousness-type double patenting rejection over applications numbers 11/059,535, 10/515,373, and 11/547,759 be withdrawn.

## VIII. CONCLUSION

This application is now believed to be in condition for allowance. If there are any outstanding issues that the Examiner believes may be appropriately addressed in a personal or telephone interview, he is respectfully requested to contact the undersigned at the telephone number below.

While it is believed that no fees are due, the Commissioner is hereby authorized to charge any necessary fees including extension of time fees, except for the Issue Fee and Publication Fee, to Deposit Account 50-0310. The Commissioner is also requested to credit any overpayments to Deposit Account 50-0310.

Respectfully submitted,
**COOLEY GODWARD KRONISH LLP**

Dated: April 28, 2008 By: _____
Mark L. Haynman
Reg. No. 51,793

Cooley Godward Kronish LLP
ATTN: Patent Group
777 6th Street, 11th Floor
Washington D.C. 20001
Tel: (202) 842-7800
Fax: (202) 842-7899

**CUSTOMER NO. 58249**